Biomarker Identification for Personalized Cardiovascular Interventions

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Abstract

Background: Cardiovascular disease (CVD) is a leading cause of death and morbidity worldwide, accounting for approximately 17 million deaths annually. Despite advances in understanding its risk factors, many patients present with CVD without established risk indicators, suggesting the presence of previously undetected pathogenic processes and genetic predispositions. Identifying novel cardiovascular biomarkers offers a promising avenue for personalized treatments that address these unknown factors and improve patient outcomes. Methods: This review explores emerging cardiovascular biomarkers that provide enhanced predictive value for ischemic heart disease beyond conventional markers. The analysis includes a review of biomarkers' roles in clinical and laboratory settings, emphasizing their ability to capture the molecular complexity of CVD. This study evaluates the clinical utility of these biomarkers in creating tailored cardiovascular therapies, ranging from targeted pharmacologic interventions to personalized lifestyle modifications. Results: Newly identified cardiovascular biomarkers demonstrate superior predictive capabilities compared to traditional biomarkers. They reveal distinct molecular signatures associated with CVD, enabling more refined diagnosis, risk stratification, and patient management. Personalized therapies informed by these biomarkers show potential for optimizing treatment outcomes, improving efficacy, and reducing adverse effects. Conclusion: Biomarker discovery is transforming cardiovascular care by integrating molecular insights into clinical decision-making. Utilizing novel biomarkers to inform personalized treatment strategies represents a paradigm shift toward more precise, effective, and patient-centric approaches to cardiovascular therapy. As we move further into the era of personalized medicine, incorporating these biomarkers into routine practice will enhance the accuracy and success of patient outcomes.

Keywords: Biomarkers, Cardiovascular Diseases, Personalized Medicine, Diagnostics, Precision Medicine.

Significance | Emerging biomarkers enhance early detection and personalized treatment of cardiovascular disease, crucial for managing subclinical conditions and improving outcomes.

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1. Introduction

Over the last three decades, cardiovascular disease (CVD) has emerged as a leading cause of morbidity and mortality worldwide, reflecting a continuous and concerning rise in its prevalence (Roth et al., 2020). By the time CVD is diagnosed, the subclinical phase of the disease often has already caused significant, often irreversible damage (Vasan et al., 2016). Current approaches to managing coronary artery disease (CAD) predominantly rely on identifying and mitigating risk factors such as hypertension, diabetes, and dyslipidemia—key contributors to atherosclerotic disease and cardiovascular events. However, up to 27% of individuals who experience their first myocardial infarction lack traditional modifiable risk factors, presenting a substantial diagnostic challenge (Figtree et al., 2021). Additionally, there is considerable variability in disease susceptibility among those classified as having

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moderate to high risk (Topel et al., 2019). Thus, identifying a biomarker that accurately reflects atherosclerosis, particularly the vulnerable characteristics of plaques, would represent a significant advancement in CAD management.

As our understanding of the complexity of cardiac diseases expands, so too must our capacity to detect and quantify these complexities. Increasingly, CVD is viewed not as a linear progression of disease but as a spectrum of interconnected processes (Smith et al., 2015). A biomarker that closely correlates with the burden of disease in a specific patient could accelerate the shift toward personalized medicine, allowing for tailored therapeutic interventions. Many contemporary biomarkers for CVD have been identified due to their pathophysiological significance, aided by high-throughput technologies, omics, and unbiased studies (Figtree et al., 2021).

This article provides an overview of recently developed cardiac biomarkers and biomarker panels, which can be measured from simple peripheral blood samples at various stages in the translational pipeline. It also considers the commercialization landscape that influences these developments. Additionally, the article reviews the possibilities, challenges, and viability of the emerging cardiovascular biomarker field, with a special focus on the detection of subclinical disease and the commercial implications of regulation and patenting. This is crucial for understanding the pathways that accelerate patients' access to the potential benefits of new biomarkers.

2. Emerging Biomarkers and Biomarker Panels for Diagnosis, Prognosis, and Quantification of Cardiovascular Disease

The development, validation, and commercialization of novel cardiovascular biomarkers involve multiple steps, including extensive preclinical and clinical testing. These biomarkers have been categorized according to the pathophysiological processes with which they are associated: cardiometabolic disease, myocardial ischemia, fibrosis and remodeling, abnormal hemodynamics and contractility, and atherosclerosis and platelet dysfunction (Figure 1, 2). These categories are interconnected, and the precise mechanisms of many biomarkers remain unclear. Table 1 summarizes recent patents in these fields, highlighting the rapid advancement in this area. In certain advanced contexts, multiple biomarker panels are employed to compute scores that guide specific therapeutic options; these are further elaborated in the section on biomarker panels for directing therapy.

3. Biomarkers of Atherosclerosis, Plaque Burden, and Platelet Dysfunction

Approximately 75% of acute coronary events are associated with the rupture of atherosclerotic plaques (Li et al., 2021). However, assessing an individual's unique risk of plaque rupture remains challenging. While percutaneous and radiographic techniques exist to measure plaque burden, each has its limitations (Maurovich-Horvat, 2014). Blood biomarkers that reflect the degree of atherosclerosis, plaque stability, and platelet dysfunction could provide a more comprehensive and individualized assessment of occlusive risk without the need for invasive procedures. These biomarkers may also more accurately identify patients who could benefit from invasive assessments (Table 1).

4. Matrix Metalloproteinase-9 (MMP-9)

Matrix metalloproteinase-9 (MMP-9) is an extracellular matrix proteinase overexpressed in stressed endothelial tissue and is associated with plaque structure and content (Jiang et al., 2014). MMP-9 is also linked with vascular endothelial growth factor (VEGF), which promotes neovascularization and further destabilizes plaques. Virtual histology-intravascular ultrasonography (VH-IVUS), an invasive technique, uses radiofrequency backscatter patterns to assess plaque burden, composition, and vulnerability during coronary angiography. In a study involving 32 patients with stable coronary artery disease, VH-IVUS identified unstable plaque characteristics, including increased necrotic core volume and fibro-fatty content, in those with elevated MMP-9 levels (Ezhov et al., 2019). Furthermore, circulating MMP-9 levels have been linked to femoral intima-media thickness, although data on carotid plaques are inconsistent (Olson et al., 2014).

In a cohort of 343 acute coronary syndrome (ACS) patients requiring intensive care, MMP-9 levels were predictive of short-term mortality, while both MMP-9 levels and their rate of change post-recovery predicted the risk of a second major cardiac event over a six-year follow-up period (Lahdentausta et al., 2018). Similarly, baseline plasma MMP-9 levels were associated with the incidence of first-time coronary disease over an eight-year follow-up in 866 middle-aged individuals, even after adjusting for traditional risk factors, high-sensitivity C-reactive protein (hsCRP), and interleukin-6 (IL-6) (Garvin et al., 2015).

5. Adiponectin

Adiponectin is a peptide hormone with cardiometabolic protective properties, produced by adipose tissue (Lui et al., 2019). It enhances insulin sensitivity and regulates lipid and glucose metabolism (Yanai et al., 2019). A cross-sectional study of 284 individuals found that lower circulating adiponectin levels were associated with metabolic syndrome, even after adjusting for confounding factors such as serum cholesterol and insulin levels (Ntzouvani et al., 2016). Given the predictive role of metabolic syndrome in the onset of arteriovascular events, this association is significant (Mathieu et al., 2016). It is also believed that serum adiponectin levels directly inhibit atherosclerosis by blocking key steps in atheroma development, enhancing endothelial cell function, and preventing

smooth muscle proliferation and foam cell formation (Yanai et al., 2019). A case-control study involving 306 participants (205 controls, 101 cases) demonstrated that lower adiponectin levels were associated with coronary artery calcification progression (Maahs et al., 2015).

6. P-selectin

P-selectin, a cell-surface adhesion molecule found on leukocytes, platelets, and endothelial cells, is associated with plaque formation (Song et al., 2020). When platelets are activated, P-selectin binds to P-selectin glycoprotein ligand-1 (PSGL-1) on leukocytes, promoting pro-thrombotic pathways, including tissue factor overexpression and stabilization of platelet-platelet contacts necessary for aggregation (Merten et al., 2014). In a cohort of 345 seemingly healthy women, those with higher soluble P-selectin levels had a 2.2-fold increased risk of experiencing a CVD event over 3.5 years compared to age- and sex-matched peers (Ridker et al., 2011). Additionally, platelet P-selectin levels were significantly higher in ACS patients compared to those with stable angina, and both were elevated compared to healthy controls, in a sample of 142 patients under 55 years old with confirmed CAD (George et al., 2016). The development of a biomarker panel or marker of atherosclerotic stability detectable in peripheral blood could pave the way for risk stratification or population-based screening to assess the likelihood of myocardial infarction or plaque rupture. However, whether the combination of these markers offers additional predictive value for short- or long-term plaque rupture risk remains uncertain.

7. Biomarkers of Myocardial Ischemia

Inflammation is a critical factor not only in atherosclerosis and vascular dysfunction but also in the initial response to myocardial ischemia. These inflammatory processes can precede acute coronary syndromes (ACS) or occur within minutes of onset, making inflammatory mediators particularly appealing as biomarkers for early detection of acute cardiac events (Bartekova et al., 2018) (Table 2).

7.1 Macrophage Migration Inhibitory Factor (MIF)

Macrophage migration inhibitory factor (MIF) is an inflammatory cytokine involved in the early cardiac response to ischemia (Luedike et al., 2018). MIF levels were elevated in a mouse model of infarction within 15 minutes of occlusion and before visible infarction, remaining high at 60 minutes. In a human study of 374 patients with ST-elevation myocardial infarction (STEMI), MIF was the only biomarker associated with infarct size, ejection fraction, and ventricular volumes on cardiac MRI at 3 days and 3 months post-infarction (Chan et al., 2013).

7.2 Nourin-Dependent miRNAs

Nourin is a potent chemoattractant peptide released from ischemic myocardium within five minutes of a heart attack (Elgebaly et al., 2019). In a cohort of patients undergoing stress echocardiography or electrocardiography testing, two specific miRNAs (miR-137 and miR-106b-5p) showed significant elevation at baseline in patients with inducible ischemia, with fold changes exceeding 1,000 and 100, respectively, compared to both STEMI patients and healthy controls (Elgebaly et al., 2021). The study also demonstrated a significant difference in miR-137 levels between STEMI patients and those with positive stress tests, suggesting these miRNAs could distinguish between normal, ischemic, and infarcting myocardium. While research into the role of these miRNAs in the heart is ongoing, miR-137 has been implicated in other inflammatory states (Elgebaly et al., 2019).

7.3 Biomarkers of Fibrosis and Myocardial Remodeling

In response to prolonged ischemia, the myocardium undergoes pathological changes, including remodeling, which directly affects myocardial function and structure. The study and validation of biomarkers that reflect these processes, such as galectin-3, soluble ST2 (sST2), and growth differentiation factor-15 (GDF-15), are crucial for assessing the extent of myocardial damage, predicting outcomes, and directing therapies (Table 3).

7.4 Hemodynamics and Myocardial Contractility

Heart disease is characterized by compromised myocardial contractility and/or relaxation, conditions often described in the context of heart failure (Figure 3). One such condition is asymptomatic left ventricular dysfunction (ALVD), also known as "pre-heart failure," which lacks suitable screening tools (Echouffo-Tcheugui et al., 2016). In a randomized sample of 75-year-olds, the prevalence of ALVD was reported to be 6.8%, with men and individuals with coronary artery disease, hypertension, or abnormal ECG results at higher risk (Zdrojewski et al., 2016). Given the association of cardiac contractility with heart failure symptoms—particularly in heart failure with reduced ejection fraction (HFrEF)—and the four-fold increase in mortality associated with ALVD over a six-year period, quantifying cardiac contractility and understanding the underlying molecular mechanisms are crucial to mitigating disease progression.

7.5 Circular RNAs, Including MICRA

Circular RNAs (circRNAs) have gained prominence as potential biomarkers for cardiac conditions due to their increased resistance to degradation compared to other components of the blood transcriptome (Sun et al., 2020). One specific circRNA, the myocardial infarction-associated circular RNA (MICRA), has shown promise as a predictive marker following myocardial infarction (MI). While its pathophysiological or functional significance remains partially understood, MICRA levels have been shown to correlate with ejection fraction in patients four months

Table 1. Summary of CVDs Biomarker of Atherosclerosis, plaque burden, and platelet dysfunction

Biomarker	Class	Role in health/disease	Measured outcome	Stage
MMP-9	Endopeptidase	Cleaves extracellular matrix proteins as part of cardiac remodelling	Predicts plaque stability compared to ultrasound and FDG-PET	Prospective observational studies
Adiponectin	Peptide hormone	Has a protective cardiometabolic effect and inhibits atheroma formation	Negatively correlates with coronary artery calcification and metabolic syndrome	Prospective observational study
P-selectin	Protein	Pro-inflammatory cytokine Platelet aggregation Increases issue factor	Predicts CVD in healthy populations Stratifies ACS, stable angina, healthy controls	Prospective observational (case-control) studies
sLOX-1 and LOX-1 ligand containing ApoB (LAB)	Protein	OxLDL receptor, triggers atherogenic pathways, contributes to inflammation and fibrosis	Complexity of coronary lesions, number of vessels implicated, stability of disease. Predict cardiac or cerebral infarction	Prospective observational study

Table 2. Summary of CVDs Biomarker of Myocardial ischaemia

Marker	Class	Role in health/disease	Measured outcome	Stage
MIF	Protein	Pro-inflammatory cytokine released in response to myocardial ischaemia	Early marker of infarct size Predicts EF and ventricular volumes on follow up CMR	Mixed retrospective and prospective observational study
miR-137 and miR-106b-5p	Micro RNA	Nourin-dependent miR with regulatory role in cell development and apoptosi	Stratifies between normal, positive cardiac stress test, and infarctio	Prospective discovery study

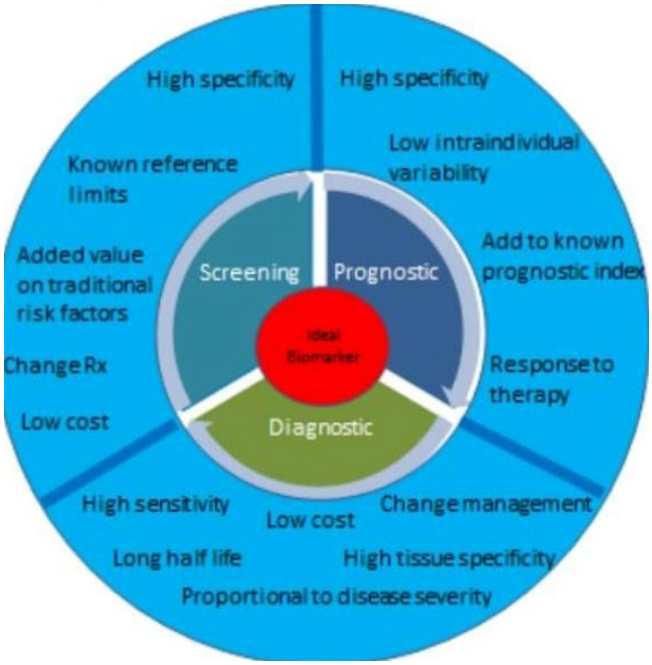


Figure 1. Ideal characteristics of a biomarker according to their intended use.

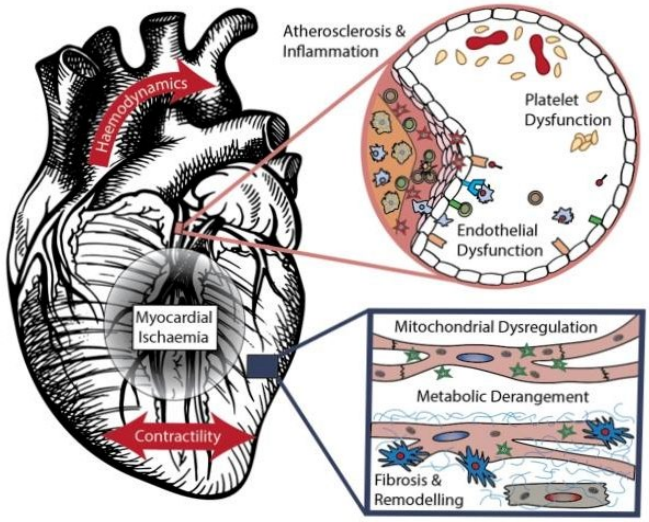


Figure 2. Mechanisms of cardiovascular disease – components modified from (10) with permission

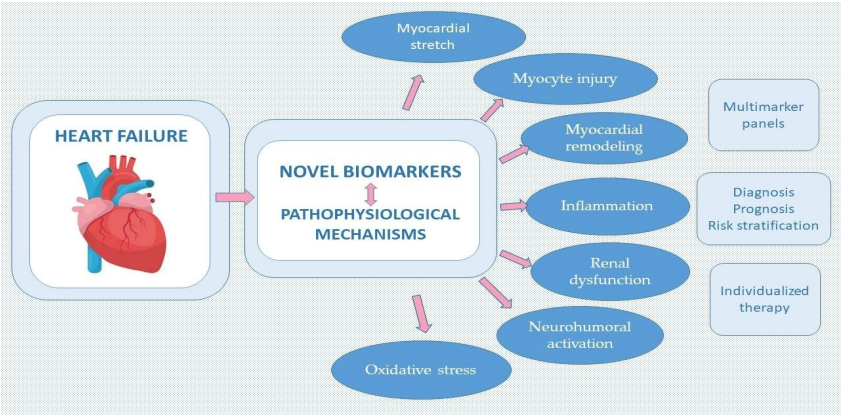


Figure 3. Hemodynamics and Myocardial Contractility

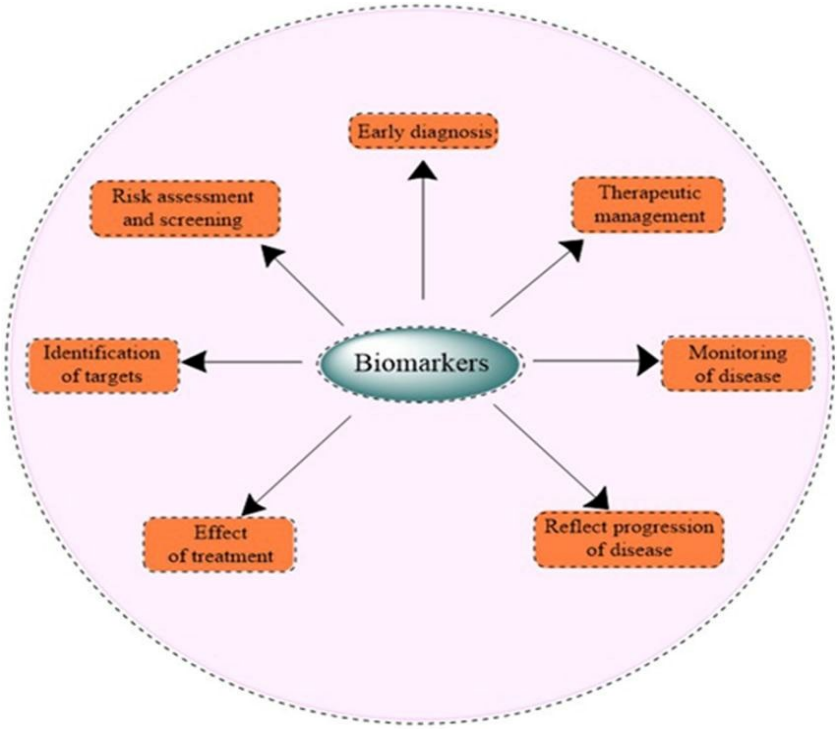
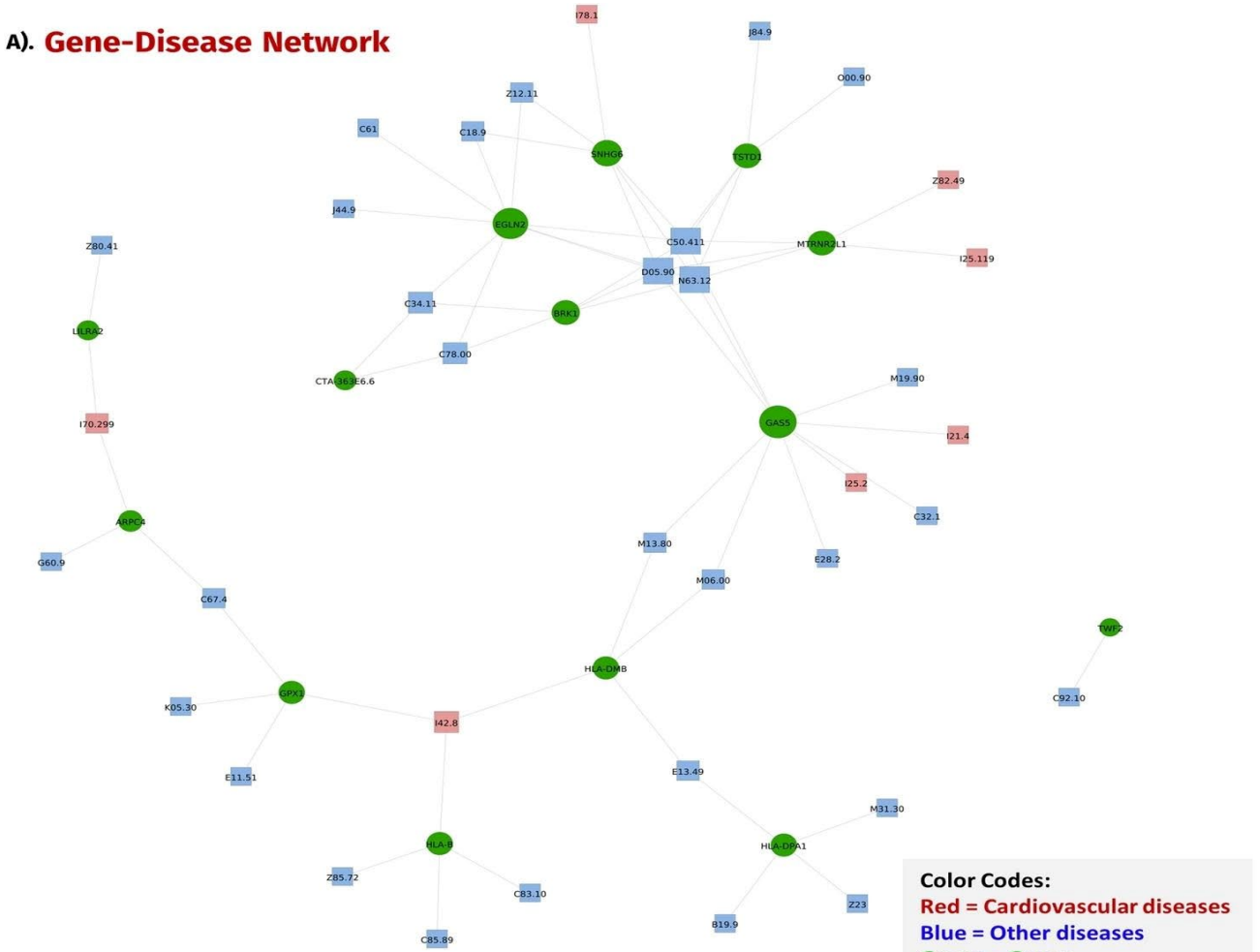


Figure 4. Applications of Novel Biomarkers Across Different Clinical Settings



B). Gene-Disease Integration

Diagnosis	ICD9	ICD10	Gene					
Type 2 or unspecified diabetes mellitus with peripheral circulatory disorder [Type 2 Diabetes]	250	E11.51	GPX1					
Osteoarthritis [Osteoarthritis]	715	M19.90	GAS5					
History of non-Hodgkins lymphoma [Diffuse Large B-cell Lymphoma]**	V10	Z85.72	HLA-B					
Malignant neoplasm of upper-outer quadrant of right female breast. unspecified estrogen receptor status (CMS/HCC) [Breast Cancer]	174	C50.411	MTRNR2L1	GAS5	TSTD1	EGLN2	SNHG6	BRK1
Seronegative arthritis [Rheumatoid Arthritis]**	716	M13.80	HLA-DMB	GAS5				
Mass of upper inner quadrant of right breast [Breast Cancer]	611	N63.12	MTRNR2L1	GAS5	TSTD1	EGLN2	SNHG6	BRK1
Coronary artery disease involving native heart with angina pectoris. unspecified vessel or lesion type (CMS/HCC) [Coronary Artery Disease]	414	I25.119	MTRNR2L1					
Special screening for malignant neoplasms. colon [Colorectal Cancer]	V76	Z12.11	EGLN2	SNHG6				
Seronegative rheumatoid arthritis (CMS/HCC) [Rheumatoid Arthritis]	714	M06.00	HLA-DMB	GAS5				
Family history of ovarian cancer [Ovarian Carcinoma]	V16	Z80.41	LILRA2					
Malignant neoplasm of upper lobe. right bronchus or lung (CMS/HCC) [Lung Cancer]	162	C34.11	EGLN2	BRK1	CTA-363E6.6			
Other malignant lymphoma of extranodal or solid organ sites [Diffuse Large B-cell Lymphoma]**	202	C85.89	HLA-B					
Other diabetic neurological complication associated with other specified diabetes mellitus (CMS/HCC) [Type 1 Diabetes]	249	E13.49	HLA-DMB	HLA-DPA1				
NSTEMI (non-ST elevated myocardial infarction) (CMS/HCC) [Myocardial Infarction]	410	I21.4	GAS5					
Obscure cardiomyopathy of Africa (CMS/HCC) [Cardiomyopathy]	425	I42.8	HLA-DMB	HLA-B	GPX1			
Other atherosclerosis of native artery of extremity [Atherosclerosis]	440	I70.299	ARPC4	LILRA2				
Family history of ischemic heart disease [Coronary Artery Disease]	V17	Z82.49	MTRNR2L1					
Wegeners granulomatosis (CMS/HCC) [Granulomatosis with Polyangiitis]	446	M31.30	HLA-DPA1					
Mantle cell lymphoma (CMS/HCC) [Diffuse Large B-cell Lymphoma]**	200	C83.10	HLA-B					
Viral hepatitis [Chronic Hepatitis B Virus]**	070	B19.9	HLA-DPA1					
Hereditary and idiopathic peripheral neuropathy [Neurodevelopmental Disorders]**	356	G60.9	ARPC4					
Malignant neoplasm of posterior wall of bladder (CMS/HCC) [Bladder Cancer]	188	C67.4	ARPC4	GPX1				
Carcinoma in situ of breast [Breast Cancer]	233	D05.90	MTRNR2L1	GAS5	TSTD1	EGLN2	SNHG6	BRK1
Need for prophylactic vaccination and inoculation against viral hepatitis [Chronic Hepatitis B Virus]**	V05	Z23	HLA-DPA1					
Polycystic ovaries [Polycystic Ovary Syndrome]	256	E28.2	GAS5					
Malignant neoplasm of colon (CMS/HCC) [Colorectal Cancer]	153	C18.9	EGLN2	SNHG6				
Telangiectasia [Hereditary Haemorrhagic Telangiectasia]**	448	I78.1	SNHG6					
Malignant neoplasm of prostate (CMS/HCC) [Prostate Cancer]	185	C61	EGLN2					
Interstitial lung disease (CMS/HCC) [Connective Tissue Disease-Associated Interstitial Lung Disease]**	515	J84.9	TSTD1					
Chronic periodontitis [Periodontitis]	523	K05.30	GPX1					
Secondary malignant neoplasm of lung (CMS/HCC) [Lung Cancer]	197	C78.00	EGLN2	BRK1	CTA-363E6.6			
Squamous cell cancer of epiglottis (CMS/HCC) [Oral Squamous Cell Carcinoma]	161	C32.1	GAS5					
Chronic obstructive pulmonary disease. unspecified COPD type (CMS/HCC) [Chronic Obstructive Pulmonary Disease]	496	J44.9	EGLN2					
Chronic myeloid leukemia (CMS/HCC) [Acute Myeloid Leukemia]**	205	C92.10	TWF2					
Ectopic pregnancy without intrauterine pregnancy [Development of Ectopic Pregnancy]	633	O00.90	TSTD1					
Old myocardial infarction [Myocardial Infarction]	412	I25.2	GAS5					

Figure 5. Gene-disease network. This figure presents a gene-disease network including linked ICD-9 and ICD-10 codes.

post-reperfusion, suggesting its utility in post-MI management (Salgado-Somoza et al., 2017). Future studies are necessary to explore the role of other circRNAs in ischemia/reperfusion injury, cardiac aging, fibrosis, and remodeling (Altesha et al., 2019).

7.6 Leukocyte-Derived Gene Biomarker Panel

ALVD is a significant risk factor for symptomatic heart failure. It can be identified by imaging modalities like tissue Doppler echocardiography, but such tests are not practical for mass screening of asymptomatic populations (Kuznetsova et al., 2010). Research has identified a panel of seven genes (FECH, TMEM79, FBXW7, NGFB, ALK, UBN1, and SLC43A2) in peripheral blood that could provide a biomarker profile for pre-clinical heart failure. This panel has demonstrated an 87% accuracy and 100% precision in predicting ALVD (Smeih et al., 2011). The genes identified encode transcription factors, membrane proteins, and mitochondrial elements not previously associated with heart disease prognosis, presenting new avenues for exploration. By contrast, NT-proBNP has limited positive predictive value but is effective in ruling out ALVD (Betti et al., 2019).

7.7 Ang2 and TSP2

Angiopoietin-2 (Ang2) is a complex regulator of angiogenesis that can exhibit both pro- and anti-angiogenic activity depending on the molecular environment. Ang2 also affects vascular permeability through pericyte detachment in inflammatory states (Akwii et al., 2019). Thrombospondin-2 (TSP2), another biomarker, acts as a potent anti-angiogenic factor while maintaining myocardial matrix integrity (Egerstedt et al., 2019).

Proteomic analysis identified Ang2 and TSP2 as promising biomarkers in a cohort of 1,315 patients, demonstrating their utility in distinguishing acute heart failure from other causes of dyspnea in emergency settings, independent of NT-proBNP levels (Wells et al., 2019). Moreover, both markers were shown to predict heart disease progression over a 20-year follow-up, emphasizing their potential long-term prognostic value.

8. Biomarkers of Metabolic Derangement and Mitochondrial Dysregulation

Metabolic syndrome is a significant contributor to contemporary heart disease, with obesity and diabetes serving as common risk factors (Wende et al., 2017). However, these conditions alone do not account for all cases of cardiometabolic illness, which may go undiagnosed until cardiovascular damage becomes evident. Potential biomarkers for these metabolic changes are closely related to mitochondrial dynamics, energy processing, and lipid modifications.

8.1 Plasma Lipidomics Panel

Lipids play a crucial role in atherosclerosis, both as global mediators of inflammation and local constituents in foam cells and necrotic lipid cores (Shapiro et al., 2016). A lipidomics panel generated through liquid chromatography-mass spectrometry identified 105 lipids in a sample of 220 patients, enhancing predictive power when combined with conventional risk factors for disease categorization (Meikle et al., 2011). Sub-analyses revealed specific lipid groups, such as alkylphosphatidylethanolamine [PE(O)] and phosphatidylethanolamine plasmalogen [PE(P)], that are exclusively significant in unstable coronary artery disease (CAD).

8.2 Antibodies to MAA Adducts

Oxidative stress and lipid peroxidation are closely linked to atherogenesis and endothelial dysfunction (Daiber et al., 2020). Assessing dysregulated oxidative signaling has proven challenging, which has implications for the development of antioxidant therapies and the identification of appropriate clinical trial populations (Brancaccio et al., 2020). Lipid peroxidation produces malondialdehyde (MDA), a compound associated with endothelial dysfunction and CAD events (Bassu et al., 2020). MDA breakdown results in malondialdehyde-acetaldehyde (MAA) adducts, which are cytotoxic and pro-inflammatory, contributing to atherogenesis (Nakamura et al., 2017). Different antibody isotypes to MAA adducts have been linked to distinct CAD states, indicating their potential as diagnostic markers (Anderson et al., 2014).

9. Applications of Novel Biomarkers Across Clinical Settings

Biomarkers are integral to clinical cardiovascular care, spanning from primary prevention to secondary prevention and acute coronary syndrome management (Pletcher et al., 2011) (Figure 4). Current primary care screening focuses on traditional risk factors, but there is a need for biomarkers that integrate these with the host response, enabling early intervention and personalized treatment strategies.

In acute coronary syndrome (ACS), biomarkers can complement non-invasive imaging to improve diagnostic accuracy and avoid unnecessary coronary angiography (Iyngkaran et al., 2019). For secondary prevention, the use of biomarkers could provide more stringent criteria for managing LDL cholesterol and blood pressure, particularly for patients with a history of adverse cardiovascular events. Biomarkers like BNP have already proven useful in monitoring heart failure therapy, and novel biomarkers may further enhance therapeutic monitoring in tertiary prevention contexts (Selleck et al., 2017).

10. Discussion

The integration of genomic and clinical data poses significant challenges, particularly in terms of standardization and interpretation. Our novel AI/ML-ready dataset, CIGT, represents a significant step toward harmonizing these heterogeneous data types to enable more precise and reliable analyses (Abdelhalim et al., 2022). Using our AI/ML approach, we identified 18 transcriptome biomarkers associated with cardiovascular diseases (CVDs),

including three novel genes (RN7SL593P, AP003419.11, and CTA-363E6.6) that warrant further investigation. Literature review and patient data analyses revealed numerous genes with established links to CVDs, such as GPX1, HLA-B, and HLA-DMB, while others, like RPS28P7 and CTA-363E6.6, remain relatively unexplored (Figure 5).

Our study highlighted several biomarkers that are not only indicative of cardiovascular disease but also linked to other conditions, including cancer and diabetes. For instance, genes like GAS5, TSTD1, EGLN2, and BRK1 have been associated with both CVDs and breast cancer. These overlapping findings suggest the broader applicability of our AI/ML model for predicting a range of complex diseases.

Using multiple AI algorithms in combination has shown potential for yielding more accurate and actionable insights compared to single-algorithm approaches. However, the clinical application of our model requires experimental validation. Future work should focus on confirming these findings through clinical trials and expanding the model's utility to other diseases, including Alzheimer's and diabetes.

There remains a significant unmet need for a more comprehensive toolkit of blood-based biomarkers for the early detection and prevention of prevalent cardiovascular disease states. Although several novel biomarkers show promise in terms of prognostic and predictive value, more longitudinal studies are needed to correlate these markers with improved patient outcomes. Advances in molecular phenotyping and blood-based biosignatures could enable more precise patient categorization, facilitating tailored treatment approaches.

The expanding knowledge of disease characteristics provided by emerging biomarkers may also accelerate the translation of new therapeutic agents, such as small molecules and targeted RNA therapies. To overcome the barriers to biomarker translation, collaboration between academia and clinical medicine will be essential. Future efforts should focus on validating these biomarkers in large-scale studies and exploring their potential to improve patient outcomes across diverse clinical settings.

11. Conclusion

The evolving landscape of cardiovascular biomarkers holds great promise for improving diagnosis, risk stratification, and personalized treatment approaches in cardiovascular diseases. By bridging the gap between emerging biomarkers and their clinical applications, healthcare providers can enhance patient outcomes and pave the way for novel therapeutic strategies. Further large-scale studies and clinical trials are needed to validate these biomarkers, explore their integration into routine clinical practice, and determine their impact on patient care and healthcare costs.

Author contributions

M.H.O.R. and M.M.H. contributed significantly to the manuscript. M.H.O.R. was responsible for conceptualizing and designing the study, collecting data, and drafting the manuscript. M.M.H. contributed to the analysis, interpretation of the data, and critical revision of the manuscript for intellectual content. Both authors read and approved the final manuscript.

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Competing financial interests

The authors have no conflict of interest.

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